

A review of the relationship between hemagglutination inhibiting antibodies and protection against influenza virus infection

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Introduction

The hemagglutination-inhibition (HAI) test is a commonly used assay for quantifying the concentration of anti-influenza antibodies in a serum sample. The classic study by Hobson et al in 1972 identified that an HAI titer of 40 correlated with approximately 50% protection against influenza virus infection, compared to a low HAI titer [1]. Other studies have also investigated the degree of protection conferred by a titer of 40, or the titer required to confer 50% protection, some of which appear to be inconsistent with Hobson's finding. We therefore conducted a systematic review to examine evidence for the degree of protection conferred by a titer of 40.

Methods

Articles were identified from PubMed and Google Scholar using "Influenza", "Flu", "Protective", "Protection", "Protect", "haemagglutination" and "hemagglutination" as search terms on 31 July 2017. We also reviewed relevant references cited in these articles, and our own bibliography. Only articles in English were included. We selected articles that reported either i) the HAI titer corresponding to 50% protection, or ii) an estimate of the protection conferred by an HAI titer of 40. We extracted the point estimates and 95% confidence intervals (95% CI). In addition, we also extracted the vaccination status, age range of participants, and the influenza type/subtype. Heterogeneity between studies was assessed using the I^2 statistic with fixed effects models. I^2 is a preferable measurement to assess the heterogeneity among included studies, and a higher value of I^2 means a higher heterogeneity. Pooled estimates would be made if the heterogeneity is low (i.e. $\leq 25\%$).

Results

We identified 1299 titles for screening, and we identified 16 that were suitable for inclusion in our review. We classified the studies into two subgroups, including papers contained the information on: i) HAI titers value which could give 50% protection against influenza virus infection (11 studies), ii) degree of protection conferred by an HAI titer of 40 (8 studies). In the first group, the HAI titers corresponding to 50% protection against influenza virus infections in these studies had a wide range of 17 to 260 with a relatively higher heterogeneity ($I^2 = 90\%$), and a geometric mean of 115 (Figure 1). In the second group, six of eight papers which contained both point estimates and 95% CIs were included in a fixed effects meta-analysis, with the point estimates of protection conferred by an HAI titer of 40 ranging from 31% to 59% ($I^2 = 0\%$), and the overall pooled estimate was 48% (95% CI: 26%, 70%) (Figure 2).

Figure 1. Forest plot of the estimates of HAI titer corresponding to 50% protection. The HAI titer generally accepted as the threshold (40) corresponding to 50% reduction in the risk of influenza virus infections is indicated by the dashed line.

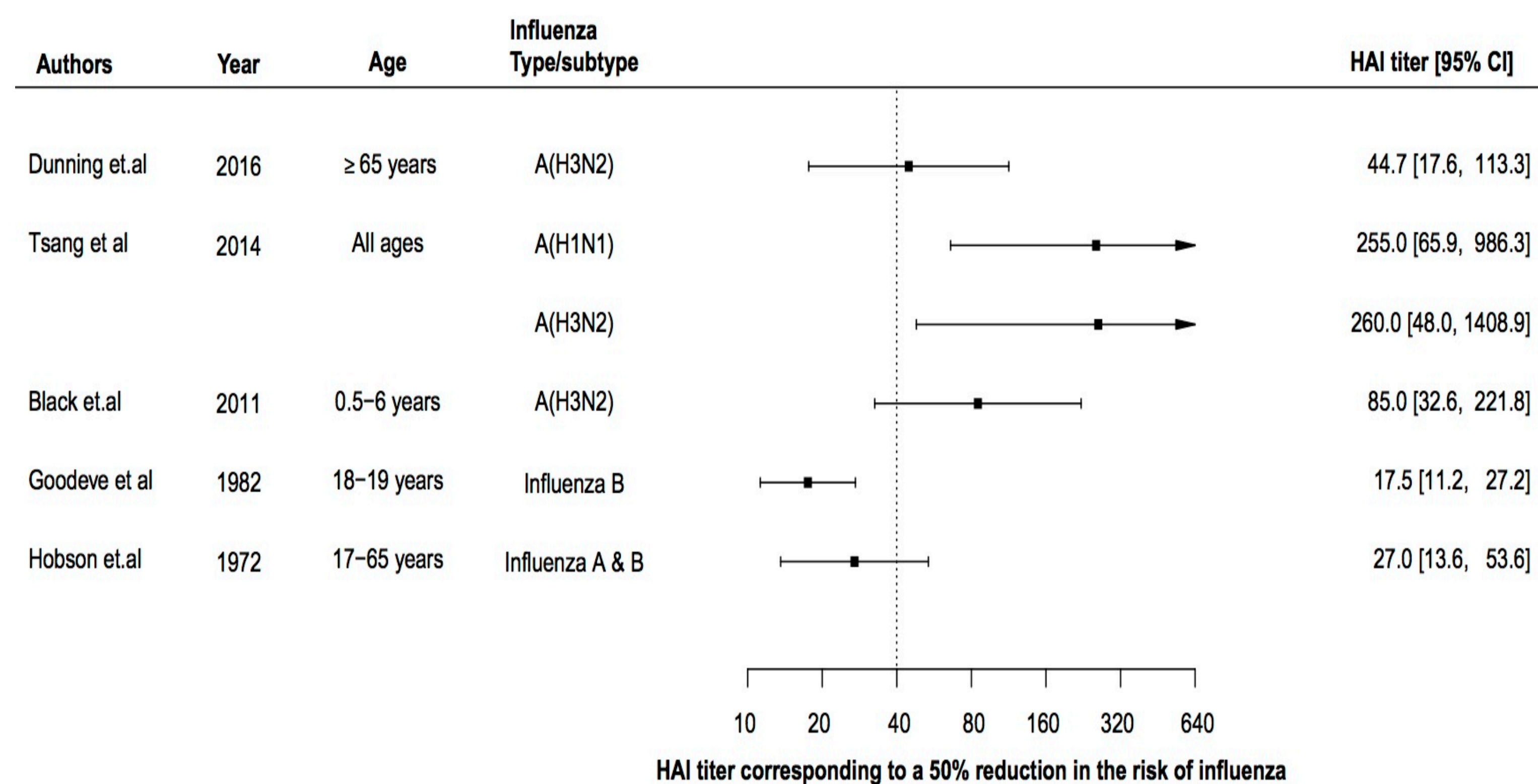
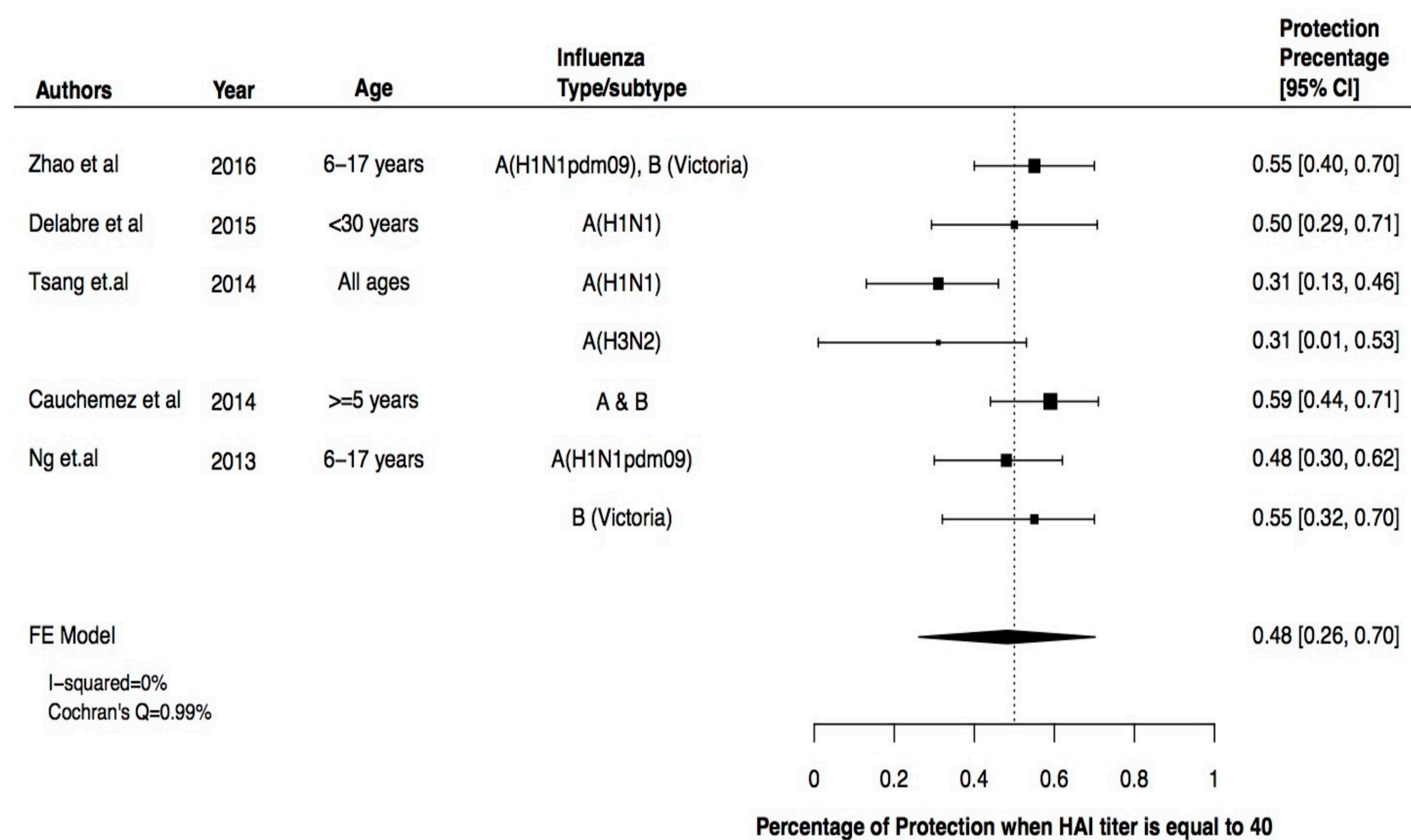


Figure 2. Forest plot of the estimates of the percentage of protection provided by HAI titer of 40.



Conclusions

We found a high heterogeneity ($I^2 = 90\%$) in HAI titer values corresponding to 50% protection rate, while a low heterogeneity ($I^2 = 0\%$) in the second group which provided the protection rates at HAI titer of 40 with a pooled estimate of 48% (95% CI: 26%, 70%). We are currently exploring whether the age, virus type/subtype, epidemic periods, and lack of standardization between the HAI assay in different laboratories contribute significantly to the heterogeneity in the estimate of the HAI titer providing 50% protection against influenza virus infection.

References

- Hobson D, Curry RL, Beare AS, Ward-Gardner A. The role of serum haemagglutination-inhibiting antibody in protection against challenge infection with influenza A2 and B viruses. *The Journal of Hygiene* 1972; 70: 767-77

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